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Clinical Research Article

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Long-Term Outcome and Treatment in Persistent and Transient Congenital Hyperinsulinism: A Finnish Population-Based Study

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Abbreviations: ^{18}F-DOPA, [18]F-fluoro-L-dihydroxyphenylalanine; CHI, congenital hyperinsulinism; IV, intravenous; P-CHI, persistent congenital hyperinsulinism; SDS, standard deviation score; T-CHI, transient congenital hyperinsulinism.

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Abstract

Context: The management of congenital hyperinsulinism (CHI) has improved.
Objective: To examine the treatment and long-term outcome of Finnish patients with persistent and transient CHI (P-CHI and T-CHI).
Design: A population-based retrospective study of CHI patients treated from 1972 to 2015.
Patients: 106 patients with P-CHI and 132 patients with T-CHI (in total, 42 diagnosed before and 196 after year 2000) with median follow-up durations of 12.5 and 6.2 years, respectively.
Main Outcome Measures: Recovery, diabetes, pancreatic exocrine dysfunction, neurodevelopment.
Results: The overall incidence of CHI (n = 238) was 1:11 300 live births (1972-2015). From 2000 to 2015, the incidence of P-CHI (n = 69) was 1:13 500 and of T-CHI (n = 127) 1:7400 live births. In the 21st century P-CHI group, hyperinsulinemic medication was initiated and normoglycemia achieved faster relative to earlier. Of the 74 medically treated P-CHI patients, 68% had discontinued medication. Thirteen (12%) P-CHI patients had partial pancreatic resection and 19 (18%) underwent near-total pancreatectomy. Of these, 0% and 84% developed diabetes and 23% and 58% had clinical pancreatic exocrine dysfunction, respectively. Mild neurological difficulties (21% vs 16%, respectively) and intellectual disability (9% vs 5%, respectively) were as common in the P-CHI and T-CHI groups. However, the 21st century P-CHI patients had significantly more frequent normal neurodevelopment and significantly more infrequent diabetes and pancreatic exocrine dysfunction compared with those diagnosed earlier.

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Conclusions: Our results demonstrated improved treatment and long-term outcome in the 21st century P-CHI patients relative to earlier.

Key Words: hypoglycemia, neurodevelopment, pancreatic exocrine dysfunction, diabetes, recovery

Congenital hyperinsulinism (CHI) is a rare disease that is characterized by inappropriate insulin secretion resulting in hypoglycemia, typically in neonates or young children (1). CHI comprises of a heterogenous group of disorders with diverse etiologies and clinical features (2). Persistent CHI (P-CHI) is considered to be a monogenic disease with an estimated incidence of 1:27 000 to 1:50 000 live births in different populations (3-5). CHI-associated mutations have been identified in at least 14 genes, most commonly in *ABCC8* or *KCNJ11* encoding the subunits of the K_{ATP} channels in the pancreatic beta cell (6). In Finland, the 2 founder variants, recessive *ABCC8*/p.V187D (7) and dominant *ABCC8*/p.E1506K (8), previously accounted for 88% of the mutation-positive patients (9). The more common transient hyperinsulinism (T-CHI) typically associates with pre- or perinatal conditions, such as maternal gestational diabetes, small birth size, or birth asphyxia (10). In addition, hyperinsulinism may appear as part of syndromic genetic disorders, such as Beckwith-Wiedemann syndrome (11).

CHI and its treatment may have significant long-term effects on the patients. Nonketotic hypoglycemia leads to a high risk of neurological impairment by blocking the formation of alternative energy sources, ie, ketone bodies, during hypoglycemia (12). Abnormal neurodevelopment has been reported in 26% to 48% of patients with P-CHI (12-16) and in 25% to 30% of patients with T-CHI (12, 16, 17). Moreover, nearly all patients have developed insulin-dependent diabetes after a near-total pancreatectomy (18, 19) which also leads to a high risk of pancreatic exocrine dysfunction (19, 20).

In the 21st century, the increased understanding of the pathophysiological mechanisms of CHI has improved the awareness of the disease and led to more individualized treatment according to drug response and genetic findings (21), compared to the former recommendations of an early radical pancreatectomy. Currently, genetic information and noninvasive [18]F-fluoro-L-dihydroxyphenylalanine (^{18}F-DOPA) positron emission tomography (PET) scan can be used to identify patients with focal CHI, which is caused by a combination of paternally inherited mutation and maternal somatic loss of heterozygosity in the affected cells and is curable by partial pancreatic resection (21-23). These patients are typically diazoxide-unresponsive and hence, radical pancreatectomy was the former choice of treatment for many of them. Diffuse CHI caused by recessive biallelic K_{ATP} mutations associating with the most severe phenotypes may still necessitate near-total pancreatectomy to avoid hypoglycemic brain damage, but medical treatment is usually effective in other genotypes causing diffuse CHI. Moreover, some patients who are unresponsive to first-line diazoxide drug therapy can be treated with second-line octreotide. (21-23) At present, it is unclear whether the improvements in management of CHI have affected the long-term outcome (12, 24-26).

In the current study, we examined the clinical characteristics, treatment, and long-term outcome of P-CHI and T-CHI from a longitudinal perspective in a large retrospective population-based cohort.

Subjects and Methods

Patients and Clinical Data

This retrospective study cohort included 238 patients with P-CHI (n = 106) or T-CHI (n = 132) who were identified by a diagnosis-based search from the patient records of the 19 largest hospitals in Finland from the period 1972 to 2015. As it is unlikely that CHI would have been diagnosed outside these hospitals, the register is representative for Finland. The median follow-up durations in the P-CHI and T-CHI groups were 12.5 years (3 months to 43 years) and 6.2 years (1 week to 19 years), respectively. The patients with P-CHI and T-CHI were from 93 and 132 different families, respectively. All patients were of Finnish ethnicity, except for 5 children in the P-CHI group.

The inclusion criteria were the diagnosis of CHI based on a combination of prolonged or recurrent hypoglycemia and signs of inappropriate insulin secretion: detectable serum insulin level and/or low free fatty acids during nonketotic hypoglycemia. Only patients who needed medication for hyperinsulinism (diazoxide or octreotide) were included. The definition of hypoglycemia was based on the recommendations of the Pediatric Endocrine Society: plasma glucose concentration ≤2.8 mmol/L (≤50 mg/dL) in the first 48 hours of life, and ≤3.3 mmol/L (≤60 mg/dL) thereafter (27). The routine screening of neonatal hypoglycemia referred to routine measurements of blood glucose within the 2 days after birth in newborns at risk.

The data were collected from the medical records by one of the authors (J.M.). We classified the patients retrospectively into the T-CHI group, when hyperinsulinism was detected during the neonatal period (<28 days after

birth) and medication was successfully discontinued within the first 4 months with no evidence of recurrent hypoglycemia during or after medication. All other patients were considered to have P-CHI. The specific genetic data was available for 95 and 58 patients with P-CHI and T-CHI, respectively, who were included in our previous genetic study by exon sequencing of 104 genes affecting glucose metabolism, including 10 CHI-associated genes (*ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HNF4A*, *HNF1A*, *SLC16A1*, *HADH*, *UCP2*, and *HK1*) (28). With respect to the longitudinal comparisons, the year 2000 was chosen as a cutoff point on the basis of markedly increased awareness of CHI due to the identification of the 2 Finnish founder variants by that time (7, 29).

Severe symptoms at onset referred to seizures or coma, and mild symptoms to any other hypoglycemia-related symptoms. Hyperinsulinemic medication referred to diazoxide or octreotide. Responsiveness to diazoxide was defined clinically, when an asymptomatic child had normal blood glucose levels and did not need intravenous (IV) glucose infusion. Recovery from CHI was defined clinically when normoglycemia sustained at the withdrawal of hyperinsulinemic medication according to repeated blood glucose measurements by fingerprick tests or continuous tissue glucose monitoring. Near-total pancreatectomy referred to ≥90% resection of pancreas for presumed diffuse CHI.

Neurodevelopmental outcome was divided into 3 groups. "Normal development" was considered when no signs of developmental problems were documented and the child attended mainstream school. "Mild difficulties" included a reported diagnosis of pervasive or specific developmental disorder (ICD-10 codes F80, Specific developmental disorders of speech and language; F81, Specific developmental disorders of scholastic skills; F82 Specific developmental disorders of motor function; F84 Pervasive developmental disorders; and F88 Other disorders of psychological development; F89 Unspecified disorder of psychological development), or a need for educational or developmental (occupational, speech or physiotherapy) support. "Intellectual disability" was defined as documented IQ < 70 (ICD-10 definition of intellectual disability, ICD-10 codes F70-F79 for intellectual disability of varying severity).

Statistical Analysis

All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Differences between continuous variables were analyzed using the nonparametric Mann-Whitney U test. The chi-square and Fisher exact tests were used to test for the associations between categorical variables. $P < 0.05$ was considered statistically significant.

Ethical Considerations

The study was approved by the local Research Ethics Committee of the Nothern Savo Hospital District and it was conducted in accordance with the Helsinki Declaration.

Results

Clinical Characteristics

The clinical characteristics are presented in Table 1. In P-CHI and T-CHI groups, the median gestational ages were

Table 1. Clinical Characteristics of the Patients With Congenital Hyperinsulinism (n = 238)

	P-CHI, all (n = 106)	T-CHI, all (n = 132)	*P*	P-CHI, before the 21st century (n = 37)	P-CHI, in the 21st century (n = 69)	*P*
Gender M / F (%)	53% / 47%	64% / 36%	0.085	54% / 46%	52% / 48%	1.000
Preterm, born before 37 weeks of pregnancy, % (n)	23.6% (25)	40.2% (53)	**0.017**	35.1% (13)	17.4% (12)	0.052
Small for gestational age, (<-2 SDS), % (n)	9.4% (10)	34.8% (46)	**<0.001**	2.7% (1)	13.0% (9)	0.159
Large for gestational age, (>2 SDS), % (n)	27.4% (29)	10.6% (14)	**0.001**	37.8% (14)	21.7% (15)	0.105
Neonatal onset of hypoglycemia, % (n)	70.8% (75)	NA	NA	73.0% (27)	69.6% (48)	1.000
Severe symptoms at detection of hypoglycemia, % (n)	21.7% (23)	0.8% (1)	**<0.001**	37.8% (14)	13.0% (9)	**0.007**
Hypoglycemia detected in routine blood glucose screening, % (n)[a]	28.3% (30)	49.2% (65)	**0.002**	16.2% (6)	34.8% (24)	**0.038**
CHI-associated gene variant, % (n)[b]	60.0% (64)	0.0% (0)	**<0.001**	73.0% (27)	56.9% (37)	0.194
Syndrome-related CHI, % (n)	7.5% (8)	5.3% (7)	0.592	0.0% (0)	12.1% (8)	0.076

Fisher exact test was used.

Abbreviations: P-CHI, persistent CHI; T-CHI, transient CHI; SDS, standard deviation score.

[a]Targeted for newborns at risk for neonatal hypoglycemia; [b]Of the patients who had specific genetic data (Persistent CHI, n = 95; transient CHI, n = 58).

38.4 (range, 27.1-42.1) weeks and 37.5 (24.0-41.9) weeks, respectively. The median birth weight standard deviation scores (SDS) in the P-CHI and T-CHI groups were 0.8 SDS (–3.3 to 7.2 SDS) and –1.3 SDS (–4.3 to 4.6 SDS) and the median birth weights 3800 g (range, 1020 to 5360 g) and 2680 g (520 to 5100 g), respectively.

The patients with P-CHI (n = 106) were more often born large for gestational age, whereas the patients with T-CHI (n = 132) were more often born small for gestational age or preterm (<37 gestational weeks).

Genetic syndromes were equally common in both groups. Trisomy 21 was diagnosed in altogether 5 (2.1%) patients (3 with P-CHI, 2 with T-CHI). Hence, it was significantly more common in this cohort (1:50) compared with the expected incidence in Finland (1:870) (30) ($P < 0.001$). Additionally, 5 patients had Beckwith-Wiedemann syndrome (2 with P-CHI, 3 with T-CHI), 1 had trisomy 13, 2 Turner mosaicism (1 with P-CHI, 1 with T-CHI), and 1 triploid mosaicism.

Genetics

We have previously reported the genetic findings of 95 and 58 patients in this cohort with P-CHI and T-CHI, respectively, based on exon sequencing of 10 CHI-associated genes (28). As a summary of the previous results, pathogenic or likely pathogenic gene variants were identified in 68% of the patients with P-CHI. K_{ATP} channel genes explained the disease in 56% (n = 53) of all P-CHI patients (5 patients with homozygous recessive, 6 with compound heterozygous recessive, 15 with heterozygous recessive founder mutation *ABCC8*/p.V187D, 14 with heterozygous dominant founder mutation *ABCC8*/p.E1506K, 3 with other heterozygous dominant variants, 6 with other heterozygous recessive variants, and 4 with a novel heterozygous variants having yet undetermined inheritance). The 2 founder mutations accounted for 58% (n = 38) of the mutation-positive patients. Additionally, 13% (n = 12) of the P-CHI patients carried a pathogenic or likely pathogenic variant in other CHI-associated genes, (including heterozygous dominant variants in *GLUD1*, n = 6; *GCK*, n = 2; *SLC16A1*, n = 3; and *HNF4A*, n = 1). None of the patients with T-CHI carried a CHI-causing gene variant.

Diagnosis

The diagnostic features are presented in Table 1. In P-CHI group, hypoglycemia was detected in the neonatal period (aged < 28 days), infancy (28 days to 1 year), and in childhood (>1 years) in 71%, 22%, and 7%, respectively, of the patients with P-CHI.

Hypoglycemia was significantly more often diagnosed in routine screening of neonatal hypoglycemia in the T-CHI than in P-CHI group ($P = 0.002$), but also in the 21st century P-CHI patients compared with the earlier patients ($P = 0.038$). Severe symptoms at the onset were significantly more common in the P-CHI group than the T-CHI group ($P < 0.001$), and more infrequent in the more recently treated P-CHI patients ($P = 0.007$). Severe symptoms at the onset were significantly more common when hypoglycemia manifested at a post-neonatal age compared with the neonatal period (61% vs 8%; $P < 0.001$).

Incidence

During the 44-year study period, the overall incidence of CHI (n = 238) was 1:11 300 live births and the incidence of P-CHI was 1:25 400 live births (Fig. 1). The incidence of P-CHI was 1:47 600 from 1972 to 1999 (n = 37) and 1:13 500 live births from 2000 to 2015 (n = 69), respectively. The first documents of hyperinsulinism which we classified as T-CHI were from 1996. Between 2000 and 2015, the incidence of T-CHI was 1:7400 live births (n = 127).

Treatment and Clinical Outcome

The details of treatment are presented in Table 2. In the P-CHI group, hyperinsulinemic medication was started at the median age of 16 days (range, 1 day to 11.3 years). Hyperinsulinemic medication was started and IV glucose infusion stopped significantly earlier in the 21st century P-CHI group compared with the P-CHI patients treated earlier (Table 2). There was no difference in the maximal glucose infusion rate between the P-CHI and T-CHI groups ($P > 0.05$).

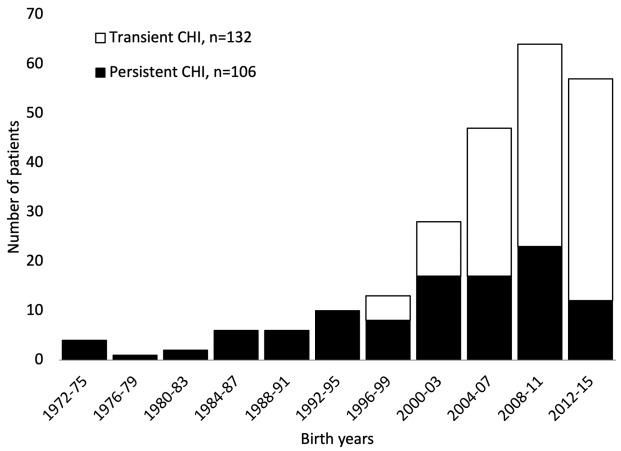

Figure 1. Number of patients diagnosed with CHI with respect to the year of birth.

Table 2. Treatment of Patients With Congenital Hyperinsulinism (n = 238)

	P-CHI, all (n = 106)	T-CHI, all (n = 132)	*P*	P-CHI, before the 21st century (n = 37)	P-CHI, in the 21st century (n = 69)	*P*
IV glucose, duration (d)[a]	12 (2-75)	6 (0-26)	<0.001[c]	22 (3-46)	8 (2-75)	0.003[c]
IV glucose, maximal rate (mg/kg/min)[a]	12.8 (4.0-25.9)	12.6 (1.9-20.0)	0.581[c]	14.1 (5.5-25.9)	12.0 (4.0-21.0)	0.505[c]
Time between the first hypoglycemia and initiation of hyperinsulinemic medication, (d)[b]	10 (0-3926)	6 (0-97)	0.012[c]	19 (1-3926)	6 (0-78)	0.010[c]
Diazoxide, maximal dose (mg/kg/d)	10.5 (3.3-34.0)	9.5 (2.1-20.1)	<0.001[c]	11.3 (3.8-34.0)	10.3 (3.3-21.0)	0.523[c]
Current medication, % (n)	22.4% (24)	NA	NA	13.5% (5)	27.1% (19)	NA
Partial pancreas resection, % (n)	12.3% (13)	NA	NA	2.7% (1)	17.4% (12)	0.030[d]
≥90% pancreatectomy, % (n)	17.0% (19)	NA	NA	51.4% (19)	0 (0)	<0.001[d]

Continuous variables are presented as median (range) values.

Abbreviations: d, day(s); P-CHI, persistent CHI; T-CHI, transient CHI.

[a]In neonates; [b]hyperinsulinemic medication referring to diazoxide or octreotide; [c]Mann-Whitney U test; [d]Fisher exact test.

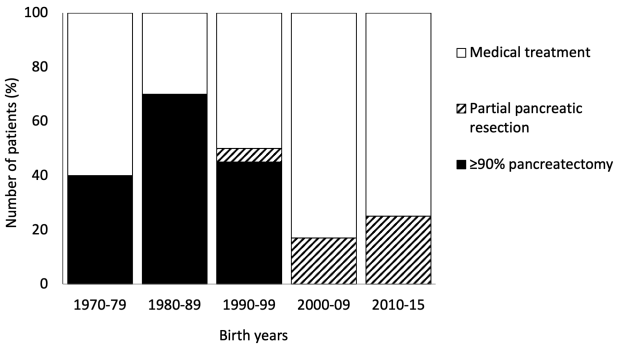

Figure 2. Treatment methods in patients with persistent congenital hyperinsulinism (n = 106).

Initially, 68% (n = 66) of the patients with P-CHI were diazoxide-responsive. Altogether, 70% (n = 74) of the P-CHI patients were treated medically (64 with diazoxide, 10 with octreotide), including also 1 patient with presumed focal CHI and 1 with a pathogenic compound heterozygous *ABCC8* variant (Fig. 2).

Thirty-two (30%) P-CHI patients underwent an operation. Of these, 13 patients had partial resection of pancreas for a suspected focal or multifocal disease at the median age of 4 months (range, 1 week to 16 months), ranging from excision of a 5-mm lesion to 80% pancreatectomy. The other 19 patients underwent near-total (≥90%) pancreatectomy for a presumed diffuse CHI at the median age of 1 month (range, 1 week to 3.5 years), including all except for 1 patient with homozygous or compound heterozygous K_{ATP} variant. Near-total pancreatectomy was not performed after year 1996, which was related to the fact that there were no patients with biallelic K_{ATP} variants.

In the T-CHI group, medication was started at the median age of 7 days (range, 1 to 102 days). All patients were diazoxide-responsive, when used, and 1 patient was treated with octreotide. The maximal diazoxide dose was significantly lower in T-CHI group compared with the P-CHI group ($P < 0.001$) (Table 2).

Long-Term Outcome: Recovery in P-CHI Group

Of the medically treated P-CHI patients, 68% (50 of 74) had discontinued medication (79% of the patients aged over 4 years [48 of 61]), the median duration of drug treatment being 3.3 years (range, 2 months to 20.2 years) (Fig. 3). The frequency of the recovered patients managing without medication did not differ between patients with or without an identified CHI gene variant ($P > 0.05$).

Twelve of the 13 patients having partial pancreatic resection were confirmed to have focal CHI and did not need hyperinsulinemic medication after partial pancreas resection, while 1 patient most likely had a diffuse disease (a slightly higher local activity detected by ^{18}F-DOPA-PET turned out to arise from a lymph node). Near-total pancreatectomy had variable effect on hyperinsulinism. Twelve (63%) of the 19 patients did not ever again need hyperinsulinemic medication, 5 patients (26%) needed an intermittent period of medication for recurrent hypoglycemia manifesting after 1 month to 2.5 years postsurgically, 1 patient (5%) was manageable with hyperinsulinemic medication, which continued immediately after the surgery, and 1 patient (5%) needed total pancreatectomy as a second operation.

Long-Term Outcome: Diabetes and Pancreatic Exocrine Dysfunction

After ≥90% pancreatectomy, 16 of 19 (84%) patients developed insulin-dependent diabetes at the median age of 5.7 years (range, 0 to 20.8 years) (Table 3). The median latest blood glycated hemoglobin (HbA1c) level was

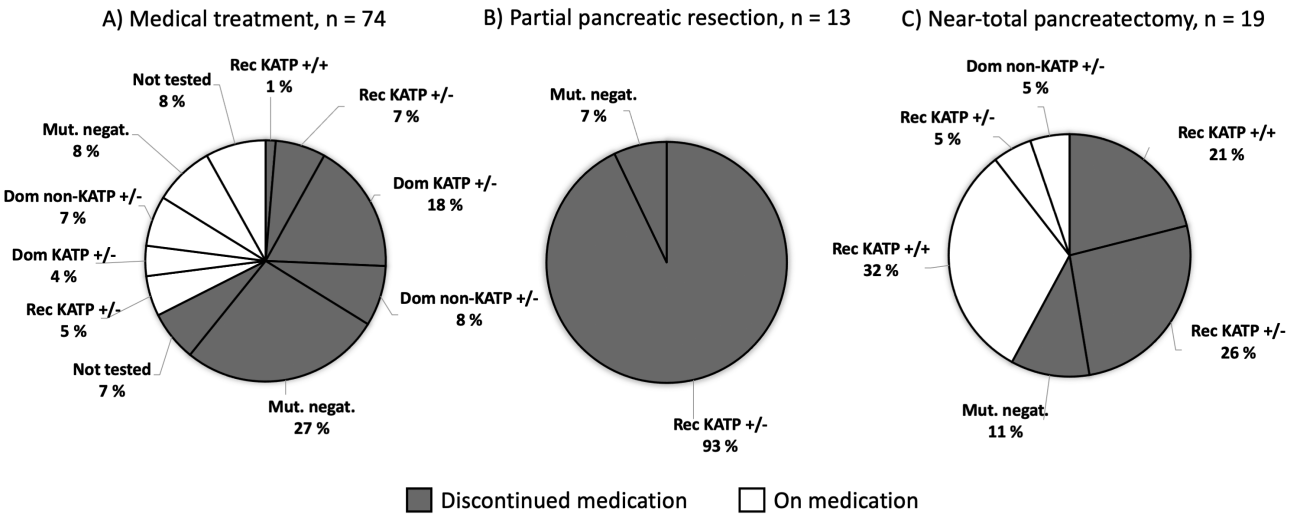

Figure 3. The frequencies of P-CHI patients who were able to discontinue hyperinsulinemic medication A) in medical treatment, B) after partial pancreatic resection for suspected focal CHI, and C) after near-total pancreatectomy for presumed diffuse CHI.

Table 3. The Long-Term Outcome in Patients With Congenital Hyperinsulinism (n = 238)

	P-CHI, all n = 106	T-CHI, all n = 132	*P*	P-CHI, before the 21st century (n = 37)	P-CHI, in the 21st century (n = 69)	*P*
Complete recovery, % (n)	77.4% (82)	NA	NA	86.5% (32)	72.5% (50)	NA
Normal development, all % (n)	69.8% (74)	79.5% (105)	0.100	48.6% (18)	81.2% (56)	0.001
Normal development, isolated CHI, % (n)[a]	75.0% (63)	90.2% (83)	0.009	51.6% (16)	88.7% (47)	<0.001
Mild developmental difficulties, all % (n)	20.8% (22)	15.9% (21)	0.400	35.1% (13)	13.0% (9)	0.011
Mild difficulties, isolated CHI, % (n)[a]	20.2% (17)	9.8% (9)	0.058	35.5% (11)	11.3% (6)	0.011
Intellectual disability, all % (n)	8.5% (9)	4.5% (6)	0.192	16.2% (6)	5.8% (4)	0.094
Intellectual disability, isolated CHI, % (n)[a]	4.8% (4)	0.0% (0)	0.050	12.9% (4)	0.0% (0)	0.016
Epilepsy, % (n)	15.1% (16)	3.0% (4)	0.002	32.4% (12)	5.8% (4)	0.001
Epilepsy, isolated CHI, % (n)[a]	14.3% (12)	0.0% (0)	<0.001	35.5% (11)	1.9% (1)	<0.001
Diabetes, % (n)	15.1% (16)	0.0% (0)	<0.001	43.2% (16)	0.0% (0)	<0.001
Clinical pancreatic exocrine dysfunction, % (n)	13.2% (14)	0.0% (0)	<0.001	29.7% (11)	4.3% (3)	<0.001

Fisher exact test was used.

Abbreviations: CHI, congenital hyperinsulinism; P-CHI, persistent CHI; T-CHI, transient CHI.

[a]In patients without other potential factors disturbing neurodevelopment than hyperinsulinism; P-CHI all, n = 84; T-CHI all, n = 92; P-CHI before 21st century, n = 31; P-CHI in the 21st century, n = 53; (excluded patients with prematurity <32 gestational weeks, severe birth asphyxia, grade 2-4 intraventricular hemorrhage, brain abnormality or damage due to other reasons, a neurological disorder or a syndrome potentially affecting the development, and inadequate data for interpretation of these factors).

75 mmol/mol (56 to 99 mmol/mol) at the median duration of diabetes of 16.8 years (1.6 to 23.8 years). None of the medically treated patients or P-CHI patients having partial pancreatic resection had diabetes. Clinical pancreatic exocrine dysfunction (ie, need for enzyme supplements) was found in 3 (23%) and 11 (58%) patients after partial resection and near-total pancreatectomy, respectively, and in none of the patients with T-CHI.

These 2 major comorbidities were significantly more uncommon in the 21st century P-CHI patients compared with the earlier patients, obviously because near-total pancreatectomies were not performed (Tables 2 and 3).

Long-Term Outcome: Neurodevelopment

The P-CHI patients treated in the 21st century had significantly more often normal neurodevelopment ($P = 0.001$), and significantly less frequently mild developmental difficulties ($P = 0.011$) and epilepsy ($P = 0.001$) compared with the P-CHI patients treated earlier (Table 3). The neurological outcome did not statistically differ between the P-CHI and T-CHI groups, except for that epilepsy was significantly more common in the P-CHI group ($P = 0.002$).

Mild neurodevelopmental difficulties were equally common in patients treated with near-total pancreatectomy (6 of 19) and partial pancreatic resection (5 of 13) (32% vs 38%, respectively), but intellectual disability was diagnosed only in the pancreatectomy group (3 of 19) (16% vs 0%, respectively).

To more specifically evaluate the hypoglycemic effect, we further analyzed the neurological outcome in a selected group of patients without other factors potentially affecting neurodevelopment: prematurity (<32 gestational weeks), severe birth asphyxia, grade 2 to 4 intraventricular hemorrhage, brain abnormality or damage due to other reasons, or a neurological disorder or syndrome potentially affecting development. Altogether, 22 (20.8%) P-CHI patients and 40 (30.3%) T-CHI patients were excluded. The proportions of normally developed children (P-CHI, 75% and T-CHI, 90%) were higher in patients having an isolated CHI as compared with the unselected groups (P-CHI, 70% and T-CHI, 80%) (Table 3).

Six patients died for several reasons. Severe hyperinsulinism was the main cause of death in 1 trisomy 21 patient with a pathogenic heterozygous *KCNJ1* variant and a contributing factor for death in 1 adult patient having a severe heterozygous *GCK* variant (31). CHI was not denoted to contribute to the death in 1 patient with the recessive founder mutation *ABCC8*/p.V187D or in the other 3 mutation-negative patients.

Associating Factors for Adverse Neurological Outcome

The P-CHI patients with abnormal neurodevelopment had significantly longer duration of IV glucose (20 vs 8 days; $P = 0.001$) and time before the initiation of hyperinsulinemic medication after the detection of hypoglycemia (14 vs 7 days; $P = 0.022$) as well as significantly more commonly severe symptoms at the onset (38% vs 18%; $P = 0.041$) and surgical treatment (41% vs 24%; $P = 0.040$) compared with the P-CHI patients with normal neurodevelopment.

In the T-CHI group, abnormal neurodevelopment associated with a longer time between the first detected hypoglycemia and initiation of hyperinsulinemic medication (8 vs 6 days; $P = 0.032$). Abnormal neurodevelopment was not associated with birth size, gestational weeks at birth, having symptoms at the onset of hypoglycemia or not, the maximal rate of IV glucose, or maximal dose of diazoxide in either group.

Discussion

We examined the diagnosis, treatment, and long-term outcome of CHI patients in a national retrospective cohort from a 44-year period, focusing on a longitudinal perspective. Long-term outcome of P-CHI has improved in respect of pancreatic endocrine and exocrine function, since all the diazoxide-unresponsive patients avoided near-total pancreatectomy due to having focal CHI or adequate response to octreotide. Furthermore, the neurological outcome was more favorable in more recently treated P-CHI patients, which is attributable to the faster achievement of normoglycemia and increased diagnosis of also milder CHI. However, the risk of adverse neurological outcome is still high in both P-CHI and T-CHI, especially when manifesting with other factors potentially disturbing neurodevelopment.

Typically, diazoxide-responsive dominant CHI was more common in this study (27% of P-CHI patients) compared with other cohorts (20% to 21%) (6, 32) due to the Finnish founder mutation *ABCC8*/p.E1506K (8). However, the other founder mutation, recessive *ABCC8*/p.V187D manifested frequently as biallelic or focal CHI causing diazoxide-unresponsive disease (28). Diazoxide-responsiveness (68%) was markedly higher compared to the largest cohort at present from Philadelphia in the United States (39%) (6) but did not differ from 2 other previous large studies (61% to 68%) (32, 33). This difference between the studies could be explained by a selection of more severe patients referred to the Philadelphia center, especially regarding focal CHI, which was more common in their study (31%) compared with ours and the 2 other studies (6% to 11%) (32, 33)

The proportion of the medically treated P-CHI patients who were able to discontinue medication (68%) fell between 61% (33) and 95% (34) reported by previous studies (both calculated from their data, excluding patients who we would have classified as having T-CHI) Although the study designs in these 3 cohorts were different, these findings indicate a high probability of spontaneous remission of drug-responsive CHI, occurring most often before school

age, but sometimes even in adulthood. The similar recovery frequency in mutation-positive and mutation-negative groups in the current study likely reflects the relatively high number of dominant CHI variants.

Interestingly, medical treatment was successful also in 2 P-CHI patients with presumed focal or multifocal lesions. In these patients, the severity of the disease and the focal signal detected by ^{18}F-DOPA-PET scan decreased during the follow-up and medication was discontinued (ages 7 months and 4 years). This self-limiting nature of focal P-CHI, also reported in a previous study (35), might possibly be explained by an increased apoptosis rate in the mutant beta cells (36). Furthermore, as we have previously reported (28), 1 patient with pathogenic compound heterozygous K_{ATP} variant and several carriers of a heterozygous missense K_{ATP} variant were treated with diazoxide.

As expected based on previous studies, partial pancreatic resection was curative in all patients with subsequently confirmed focal CHI (18, 23, 37-40) and none of these developed diabetes (18, 40). Notably, 3 patients developed pancreatic exocrine dysfunction 4 months to 8 years after a 50% to 80% resection of the pancreas after combined with Roux-en-Y, which is a common risk factor for this comorbidity (41). This contradicts a previous large clinical study which indicated normal exocrine function after partial pancreatic resection and Roux-en-Y (38), a longer follow-up period in the current study only partly explains this difference.

This study demonstrated the presumed (15) decrease in the prevalence of diabetes and pancreatic exocrine dysfunction over time, since the identification of those having focal CHI among other diazoxide-unresponsive patients has markedly decreased the need for radical pancreatectomy. Moreover, near-total pancreatectomy was not needed in Finland in the 21st century, since there were no cases with homozygous (and only 1 with compound heterozygous) K_{ATP} gene mutations associating with the most severe phenotypes (28). The results are gratifying, considering that the prevalence of diabetes (84%) and clinical pancreatic exocrine dysfunction (58%) after near-total pancreatectomy were high, consistent with previous studies (56% to 96% (18, 19, 24, 42) and 39% to 63% (19, 37, 43), respectively).

The current study also showed that P-CHI patients treated in the 21st century had better neurological outcome compared to previously treated patients. This explains the lower overall frequency of abnormal neurodevelopment in P-CHI (29%) compared to the other nationwide studies from (44% to 45%) (15, 44). Longitudinal improvement in the outcome has not emerged in previous studies (12, 24-26), except for one small cohort (n = 14) (45). The lack of the most severe phenotypes may have contributed to the results, but also our findings of increased detection of hypoglycemia before symptoms (by the advanced routine blood glucose screening in newborns at risk), as well as earlier diagnosis of hyperinsulinism and achievement of normoglycemia are attributable to the improved prognosis.

Despite the improvements, the current frequencies of abnormal neurodevelopment and epilepsy were still high and strengthened the previous findings of similar outcome in T-CHI and P-CHI (12, 17). However, hypoglycemia may not be the only determinant of the outcome (15, 46). We found that CHI manifested frequently in association of other factors potentially affecting the development (P-CHI 22%; T-CHI 30%), which may even further worsen the outcome. Interestingly, the prevalence of Down syndrome was surprisingly high, although it has not been previously reported to associate with hyperinsulinism. Encouragingly, however, the T-CHI patients and the 21st century P-CHI patients having an isolated CHI showed similar proportions of normal development as the general population and none had intellectual disability.

Nevertheless, the high risk of even mild neurological impairment in this potentially fatal disease is to be taken seriously. In our previous clinical study, the 21st century P-CHI patients without any other risk factors than hypoglycemia (a subcohort of the current study) showed narrow specific neurocognitive problems eligible for hypoglycemic origin in (16). The current study strengthened the previous observations of the association of more severe disease or delay in treatment with poorer neurological outcome (12, 15, 25, 44, 47, 48) and hence, timely diagnosis and efficient treatment are most important in the pursuit of better outcome.

The incidence of P-CHI (1:25 400 live births) was surprisingly high compared to the previous estimates (1:27 000 to 1:50 000 live births) (3, 5, 49). The incidence of T-CHI, 1:7400 live births between 2000 and 2015, was also higher compared to the previous 2 estimates of 1:12 000 to 1:17 000 live births (49, 50), although comparisons between studies are difficult because the definition of T-CHI is not generally well established. The current incidence suggests that hyperinsulinism is the cause in 1 per 7 to 25 newborns with hypoglycemia (incidence of neonatal hypoglycemia, 1-3.5:1000). Our population-based, more recent study cohort and more accurate documentation of diagnosis and improved protocol of screening of blood glucose in newborns at risk have most likely contributed to the increased incidence in the early 2000s, especially regarding T-CHI. Nevertheless, it cannot be ruled out that CHI is more common in Finland due to its genetic isolation and founder effects (49, 50).

This study has some limitations. As discussed above, it is likely that the diagnosis search did not capture all the patients with T-CHI, especially before the implementation

of ICD-10 in 1996 which provides a more specific code for hyperinsulinism. Moreover, the patients did not usually undergo a formal fasting test at the time of discontinuation of medication, which may slightly overestimate the proportion of the patients classified as "recovered." Furthermore, there was no uniform protocol for the clinical follow-up of the patients, but it was planned individually and hence, referral bias cannot be excluded regarding pancreatic exocrine dysfunction and milder neurological difficulties.

In conclusion, this retrospective nationwide study cohort demonstrated an improved overall long-term outcome of P-CHI patients over time. This is attributable to the faster recognition of hyperinsulinism, more prompt achievement of normoglycemia, and more individualized treatment of CHI. Notably, both P-CHI and T-CHI commonly occurred in combination with other conditions potentially disturbing neurodevelopment, but the neurological outcome of the patients with an isolated form of P-CHI was not strikingly different from the general population.

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